Top Organomet Chem (2016) 56: 133–154
DOI: 10.1007/3418_2015_122

Published online: 10 June 2015

# Applications of Catalytic Organometallic C($sp^3$)–H Bond Functionalization

**David Dailler, Grégory Danoun, and Olivier Baudoin**

**Abstract** The transition-metal-catalyzed activation of C($sp^3$)–H bonds has emerged as powerful strategy to create bonds and introduce functional groups in a direct fashion. This review focuses on recent applications of C($sp^3$)–H bond functionalization strategies to the synthesis of biologically active and natural compounds.

**Keywords** Bioactive molecules · C–H activation · Natural products · Total synthesis · Transition metals

## Contents



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# 1 Introduction

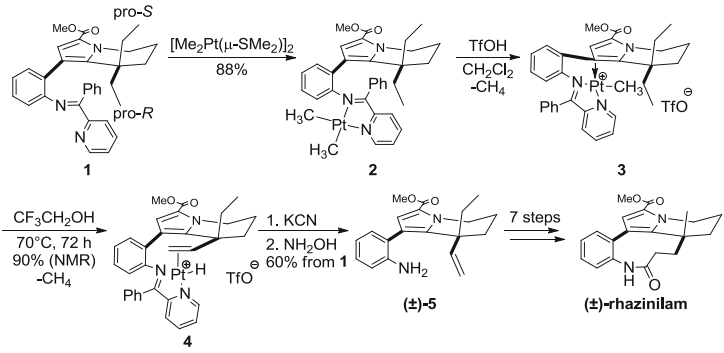
Compared to the wealth of catalytic methods which have been developed for the functionalization of C($sp^2$)–H bonds of arenes and heteroarenes, relatively little work has focused on the functionalization of unactivated, nonacidic C($sp^3$)–H bonds of alkyl fragments. Most transition-metal-catalyzed C($sp^2$)–H functionalization methods involve a C–H activation step in which a C–H bond is cleaved and a carbon–metal bond is formed, a process which has been termed "organometallic" or "inner-sphere" C–H activation [1]. But the organometallic activation of C ($sp^3$)–H bonds is generally more difficult to achieve, because these bonds are less acidic and lack proximal empty low-energy or filled high-energy orbitals that interact with filled or empty orbitals of the metal, respectively. Despite this intrinsic difficulty, considerable progress has been made in the past decade, and catalytic organometallic C($sp^3$)–H bond activation has now become a straightforward and practical tool to build C=C and C($sp^3$)–X bonds (X=C or heteroatom) in a complex molecule setting [2–5].

This chapter highlights recent remarkable examples of the fast-growing literature on the application of catalytic organometallic C($sp^3$)–H bond functionalization to the synthesis of natural products and active ingredients, of interest for medicine and agrochemistry [6–8]. Reactions involving the cleavage of activated C–H bonds, in α position to heteroatoms or electron-withdrawing groups, or which do not involve organometallic intermediates are not covered herein.

# 2 Heteroatom-Directed C–H Activation

## *2.1 Pioneering Stoichiometric Studies*

Pioneering applications of heteroatom-directed C($sp^3$)–H activation using stoichiometric amounts of metal salts were described by Sames and co-workers in the early 2000s. These studies paved the way for the development of subsequent catalytic methods. In 2000, the total synthesis of the antimitotic natural product (±)-rhazinilam was achieved using a platinum-mediated dehydrogenative C–H bond activation as key step [9]. Several seminal reports had shown that platinum complexes containing nitrogenous bidentate ancillary ligands were prone to undergo C–H activation [10–13]. Exploiting this property, Johnson and Sames employed optimized Schiff base **1** as a bidentate ligand to form the pivotal platinum complex **2** by reaction with a dimethylplatinum reagent $[Me_2Pt(\mu\text{-}SMe_2)]_2$ (Scheme 1). Treatment of **2** with triflic acid afforded a cationic platinum complex **3**, which upon heating in $CF_3CH_2OH$ provided the hydridoplatinum (II) complex **4**, resulting from the selective dehydrogenation of one ethyl group, with excellent yield (90%, NMR yield). Subsequent platinum decomplexation with aqueous KCN followed by cleavage of the imine afforded racemic alkene **5** in 60% overall yield from **1**.

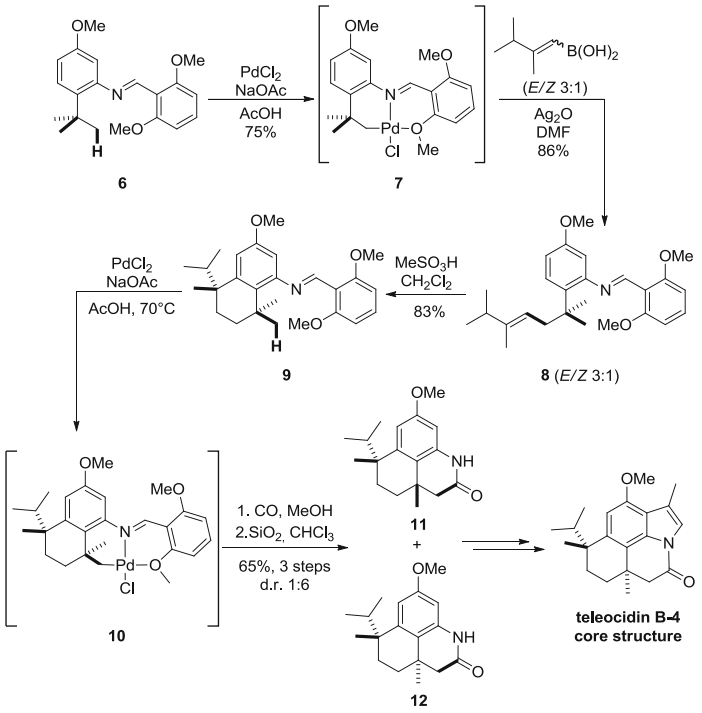



**Scheme 1** Synthesis of (±)-rhazinilam involving Pt-mediated alkane dehydrogenation

Alkene **5** was employed to synthesize (±)-rhazinilam in seven additional steps. Sames and co-workers later described an asymmetric version of this approach by differentiating the two enantiotopic ethyl groups using a chiral oxazoline-containing Schiff base [14].

After this first application of a stoichiometric alkane dehydrogenation reaction, Sames and co-workers turned to C($sp^3$)–C($sp^2$) bond formation via heteroatom-directed C($sp^3$)–H bond activation. In 2002, they described the synthesis of the core of teleocidin B4, a complex natural product fragment including two quaternary stereocenters (Scheme 2) [15]. They envisioned that a *tert*-butyl group could act as the cornerstone for the construction of this tetracyclic compound via two directed C–H bond activations. Starting from a tuned Schiff base **6** containing two methoxy substituents to avoid the metalation of arene C–H bonds, a stable six-membered palladacycle **7** was generated by treatment with a stoichiometric amount of $PdCl_2$. The isolation of this intermediate showed the bidentate coordination of the Schiff base and one *ortho*-methoxy group. Palladacycles such as **7** have been known to undergo direct functionalization reactions [16–19]. However, transmetalation with boronic acids had not been reported. Palladacycle **7** reacted with a boronic acid in the presence of $Ag_2O$ to provide the alkenylated product **8** with 65% yield from **6**. Then, treatment of **8** with methanesulfonic acid generated the cyclized product **9**, the precursor of the second C–H activation process, via a Friedel–Crafts alkylation in good yield. Stoichiometric $PdCl_2$ and NaOAc were reacted with **9** to afford a mixture of diastereoisomeric palladacycle **10**, which was directly treated with carbon monoxide and methanol to furnish methyl ester intermediates. Under acidic conditions (silica), the Schiff base was hydrolyzed, followed by spontaneous cyclization, thus providing diastereoisomeric lactams **11** and **12** (65% yield over three steps, d.r. = 1:6). The final stage of the synthesis of the teleocidin core involved indole formation, which was performed in three steps from major diastereoisomer **12**.

Through the preceding syntheses, Sames and co-workers demonstrated the potential of the heteroatom-directed C($sp^3$)–H bond activation strategy in total synthesis, which allows to draw nontraditional disconnections in retrosynthetic



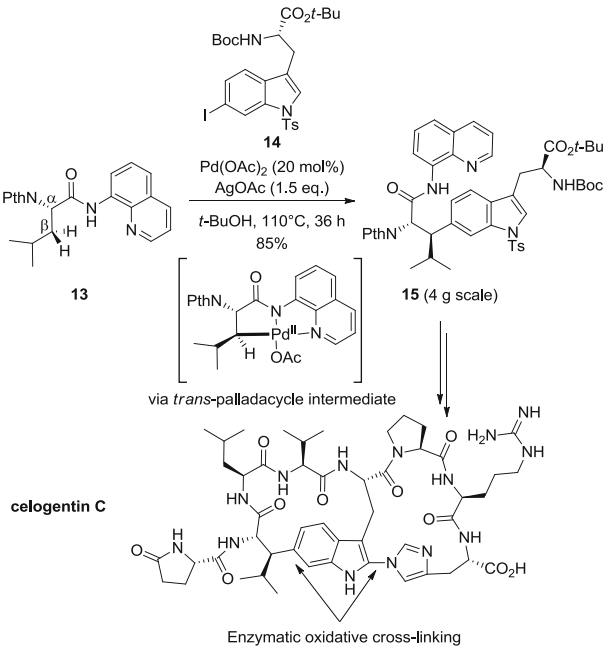

**Scheme 2** Synthesis of the core of teleocidin B-4 via multiple Pd-mediated C–H activation

analysis and to construct new bonds in a straightforward manner. However, in these pioneering studies, stoichiometric amounts of metal were necessary to perform the key transformations. Subsequent efforts were devoted to the development of catalytic methods that retain synthetic applicability.

## 2.2 *β-Arylation of Carbonyl Compounds*

In 2005, taking advantage of bidentate coordinating groups to efficiently bind to a transition metal and to position the latter in proximity to a targeted C–H bond, Daugulis and co-workers described the $Pd^{II}$-catalyzed regioselective β- and γ-arylation of unactivated $C(sp^3)$–H bonds, by introducing respectively 8-aminoquinoline and picolinamide directing groups [20, 21]. Inspired by this seminal report, numerous developments of new bidentate directing groups and methods have been subsequently reported [22].

In 2006, the group of Corey described a first extension of this concept [23]. Using the 8-aminoquinoline directing group, they could achieve the palladium-catalyzed diastereoselective β- and γ-$C(sp^3)$–H arylation of protected α-amino acid derivatives with aryl iodides and catalytic amounts of $Pd(OAc)_2$.

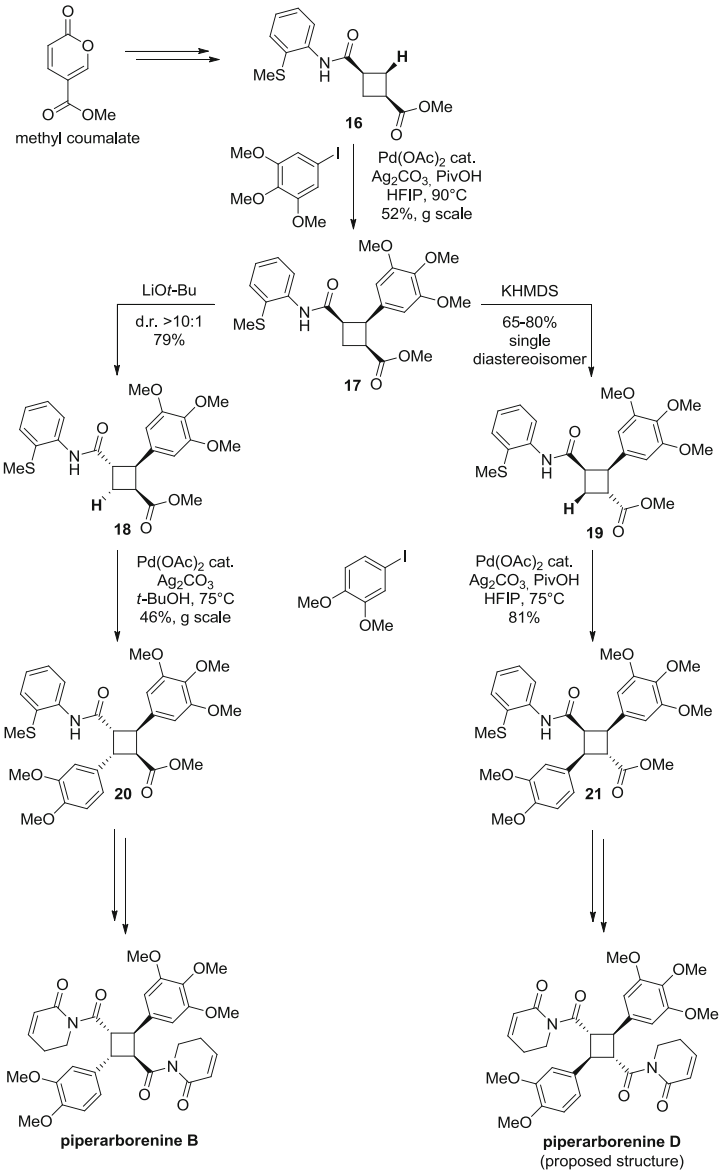



**Scheme 3** Total synthesis of celogentin C featuring Pd-catalyzed directed C–H arylation

Following up on this study, Feng and Chen achieved the total synthesis of (–)-celogentin C (Scheme 3) [24]. Inspired by the proposed biosynthesis involving enzymatic oxidative cross-links [25, 26], they envisioned to construct the Leu-Trp C($sp^3$)–C($sp^2$) bond by regio- and diastereoselective C–H arylation of the Leu motif **13**. After optimization on a model substrate, they could perform the arylation of **13** with iodide **14** in good yield on a multigram scale, using $Pd(OAc)_2$ as the catalyst and AgOAc as the terminal oxidant. A complete diastereoselectivity was observed, which was ascribed to the preferential formation of a *trans*-palladacycle intermediate avoiding the steric clash between the isopropyl and *N*-phthaloyl groups. This $Pd^{II}$ intermediate afforded, after oxidative addition of aryl iodide **14** and C–C reductive elimination, compound **15** with the *erythro* stereochemistry. Interestingly, only the *N*-phthaloyl protecting group could be successfully employed for the arylation process. However, its bulkiness and lability proved to be troublesome during the cleavage of the aminoquinoline auxiliary, for which no mild conditions had been reported. To solve this issue, Chen and co-workers carried out a three-step sequence starting with the transformation of the *N*-phthaloyl group into a smaller azide, followed by Boc-activation of the amide [27] and hydrolysis under Evan's conditions [28]. Overall, the total synthesis of celogentin C was achieved in 23 steps, featuring the first application of catalytic C($sp^3$)–H bond functionalization using a bidentate directing group in natural product synthesis.

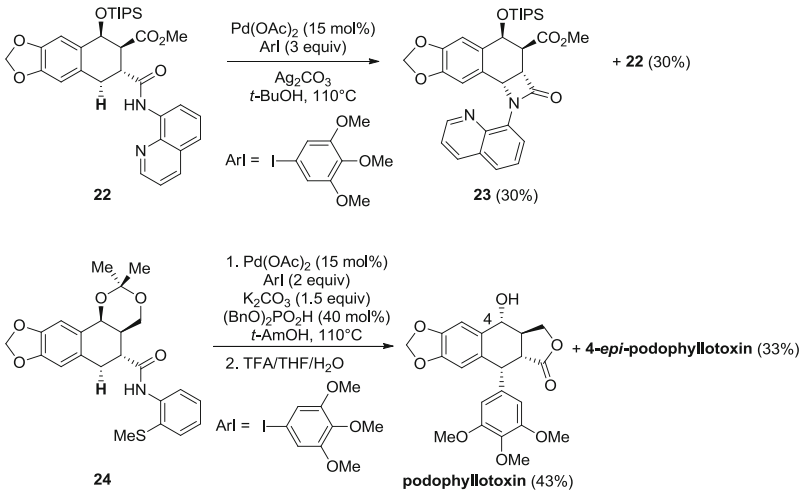
In 2011, Gutekunst and Baran described both the first example of sequential catalytic C($sp^3$)–H arylations in total synthesis and of transition-metal-catalyzed activation of C–H bonds of a cyclobutane ring [29]. This iterative C–H functionalization strategy provided an efficient access to unsymmetrical cyclobutanes of biological interest while avoiding pitfalls of classical cyclobutane synthesis via photoinduced [2+2] cross-dimerization: head-to-head and head-to-tail additions, homodimerization, and *E*/*Z* isomerization of olefin precursors, generally leading to the uncontrolled production of a complex mixture of regio- and stereoisomers [30, 31]. To achieve the synthesis of piperarborenines (Scheme 4), Baran and co-worker selected the [2-(methylthio)phenyl]carbamoyl derivative **16** instead of the 8-aminoquinoline directing group, because the hydrolysis of the former was reported to occur under milder conditions [32]. After optimization, they found that the addition of HFIP and pivalic acid [33] is critical to perform the first C($sp^3$)–H arylation with complete regio- and diastereoselectivity, to give *cis*-configured product **17** on gram scale. Taking advantage of divergent epimerization to obtain diastereoisomers **18** and **19** in good yield and stereoselectivity, they successfully performed the second diastereoselective C($sp^3$)–H arylation under similar conditions, thus affording tetrasubstituted cyclobutanes **20** and **21**. Piperarborenines B and D were then synthesized from these intermediates in 2–3 steps via transformation of the amide and ester groups into carboxylic acids, followed by condensation with dihydropyridone. Overall, this iterative C–H functionalization strategy allowed to access both natural products in 6–7 steps, 7–12% overall yield. Later on, Baran and co-workers reported an extension of this strategy to the sequential C–H arylation/alkenylation of cyclobutanes, which allowed to synthesize pipercyclobutanamide A, another congener of the same family of natural products [34, 35].

During their studies on the total synthesis of podophyllotoxin based on a Pd-catalyzed C($sp^3$)–H arylation strategy (Scheme 5) [36], Ting and Maimone reported subtle conformational effects on reductive elimination pathways. Indeed, when precursor **22** was engaged in directed C($sp^3$)–H arylation under usual conditions, β-lactam **23** was unexpectedly isolated as the major product. In the past few years, the direct C–N bond reductive elimination of the nitrogen atom of the amide directing group has been well documented [37–42]. To understand and suppress this undesired pathway, the authors carried out X-ray diffraction analyses of the acetonitrile-bound $Pd^{II}$ complex arising from the C–H activation step. They identified that the environment of this palladacycle is highly congested and affected by the conformation of the cyclohexene ring. As a consequence, they prepared the conformationally distinct substrate **24** as new a precursor of the C–H activation process. After significant optimization including the use of dibenzylphosphate as an additive [43–45], the desired C–C bond formation was performed in 58% yield. To finish, a simple treatment of the arylated product with a TFA/THF/$H_2O$ mixture afforded podophyllotoxin and C-4 *epi*-podophyllotoxin, due to the epimerizable character of the C4 stereogenic center. This strategy provided a five-step synthesis of podophyllotoxin from commercially available bromopiperonal and a straightforward entry into novel arene-modified analogues.




**Scheme 4** Total synthesis of piperarborenines via sequential Pd-catalyzed C–H arylations of a cyclobutane core

Recently, further work has been described employing the 8-aminoquinoline directing group for the efficient synthesis of *cis*-3-substituted proline derivatives [46, 47], which are compounds of interests in organocatalysis [48] and drug discovery [49–51].

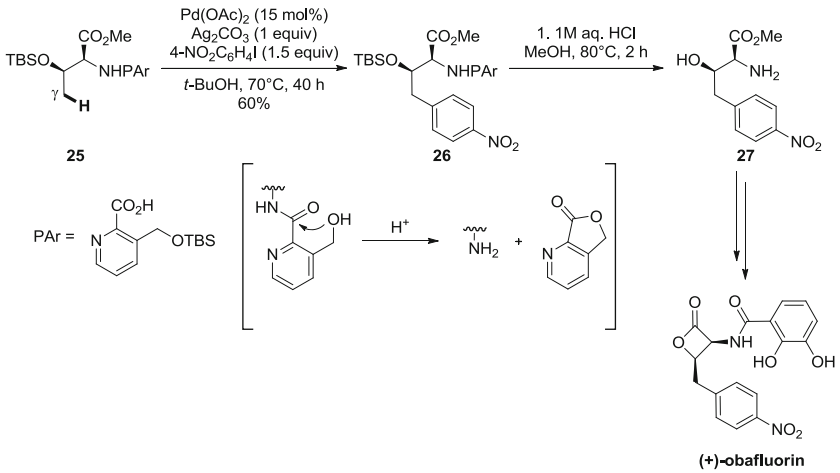



**Scheme 5** Total synthesis of podophyllotoxin via Pd-catalyzed directed C–H arylation

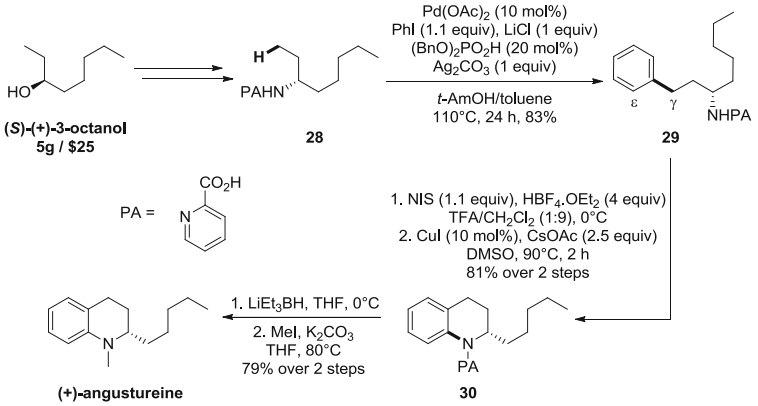
## 2.3 γ-Arylation of Amine Derivatives

Based on the original study of Daugulis and co-workers, who introduced the picolinamide bidentate directing group for the palladium-catalyzed γ-C($sp^3$)–H arylation of amine derivatives [20], He and Chen reported major improvements which facilitate synthetic applications [50]. Indeed, they developed milder conditions (80°C, with *t*-BuOH or trifluoroethanol as the solvent), which are compatible with sensitive functional groups and stereogenic centers found in complex molecule settings. Furthermore, based on precedents in peptide chemistry [52], they developed a modified picolinamide directing group which can be removed through intramolecular acyl transfer under mildly acidic conditions. The importance of these modifications was demonstrated through to the formal synthesis of (+)-obafluorin (Scheme 6). The synthetic sequence started from the readily available threonine derivative **25**, which was engaged in the optimized γ-C–H arylation conditions to afford the desired arylated product **26** in 60% yield. The directing group was then smoothly removed under acidic treatment to provide aminoester **27**, which served as an intermediate in the formal synthesis of (+)-obafluorin.

In 2013, Chen and co-workers reported a streamlined approach for the synthesis of tetrahydroquinolines (THQs) via the sequential functionalization of remote C–H bonds [53]. Starting from readily available aryl iodide and aliphatic amine precursors, this strategy involved a three-step sequence including palladium-catalyzed γ-C($sp^3$)–H arylation, followed by a previously optimized metal-free ε-C($sp^2$)–H iodination reaction [54] and a more classical Cu-catalyzed intramolecular C–N coupling. To test the efficacy of this novel procedure, the authors applied it to the total synthesis of the antimalarial alkaloid (+)-angustureine (Scheme 7) [55]. *N*-Alkylpicolinamide **28** was easily accessible from commercially available (*S*)-(+)-3-



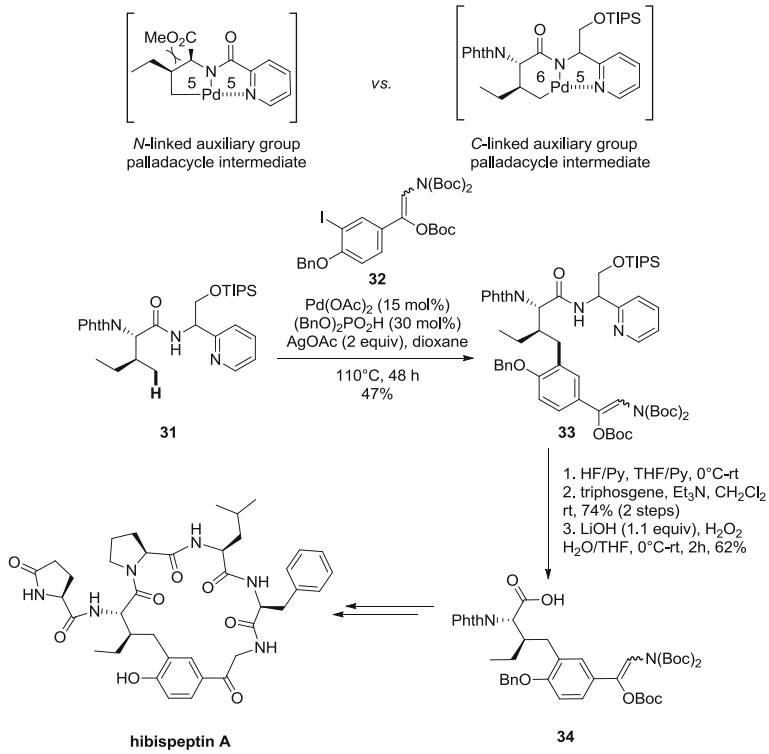

**Scheme 6** Formal synthesis of (+)-obafluorin via Pd-catalyzed directed γ-C–H arylation of a threonine derivative




**Scheme 7** Synthesis of (+)-angustureine involving Pd-catalyzed directed γ-C–H arylation

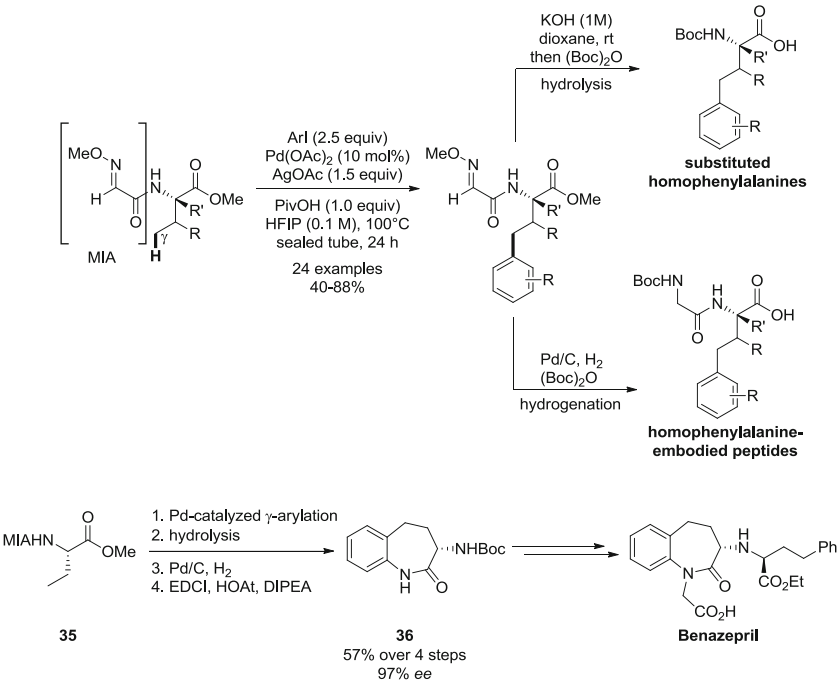
octanol. It was engaged in the directed γ-C($sp^3$)–H arylation with iodobenzene to afford the desired arylated product **29** in excellent yield. Compound **29** was then treated with NIS and $HBF_4$ to provide the corresponding *ortho*-iodinated product in mono-selective fashion, which was subsequently engaged in the Cu-catalyzed cyclization to give THQ **30** in 81% yield over two steps. Finally, removal of the PA group from the cyclized compound **30** under reductive conditions followed by *N*-methylation furnished (+)-angustureine in good overall yield.

Despite significant improvements of palladium-catalyzed directed C($sp^3$)–H arylation, including the use of less reactive but more cost-attractive aryl bromides [56] or open-air, room-temperature conditions [57], only sporadic examples of




**Scheme 8** Synthesis of hibispeptin A featuring a Pd-catalyzed directed γ-C–H arylation with a hindered aryl iodide and a removable directing group

coupling with sterically hindered aryl donors have been reported [58–61]. To address this challenge, Chen and co-workers introduced a new pyridylmethylamine-based directing group, which enabled C–H arylation with sterically hindered *ortho*-substituted aryl iodides [62]. As an illustration, to access the key Ile-Hpa pseudodipeptide moiety in hibispeptin A (Scheme 8), the authors first considered the original *N*-linked picolinamide directing group, which proved efficient in previous γ-C($sp^3$)–H arylations of amino acid substrates [20, 58]. Unfortunately, the corresponding γ-Me arylation occurred in low yield (<20%) due to a sterically disfavored *cis*-configuration of the α-$CO_2$Me and β-Et groups in the five-membered palladacycle intermediate. To solve this low reactivity issue and based on previous studies on the $\gamma-$ arylation of amino acids [23], they explored a series of *C*-linked directing groups that would induce the formation of a less hindered but also less kinetically favored six-membered palladacycle intermediate. They initially found that 2-pyridylethylamine, introduced by Chatani and co-workers [63], provided good arylation yields, but low conversions and loss of chiral integrity during the cleavage of the directing group. Based on their previous studies [58], they designed a new pyridylmethylamine-based directing group which could be




**Scheme 9** Formal synthesis of benazepril via Pd-catalyzed γ-C–H arylation using the 2-methoxyiminoacetyl (MIA) directing group

easily removed. The latter was employed to perform the γ-Me arylation of Ile derivative **31** with *ortho*-substituted aryl iodide **32**, which provided the key Ile-Hpa residue **33** in moderate yield. A three-step cleavage sequence then furnished carboxylic acid **34**, a key intermediate of the synthesis of hibispeptin A.

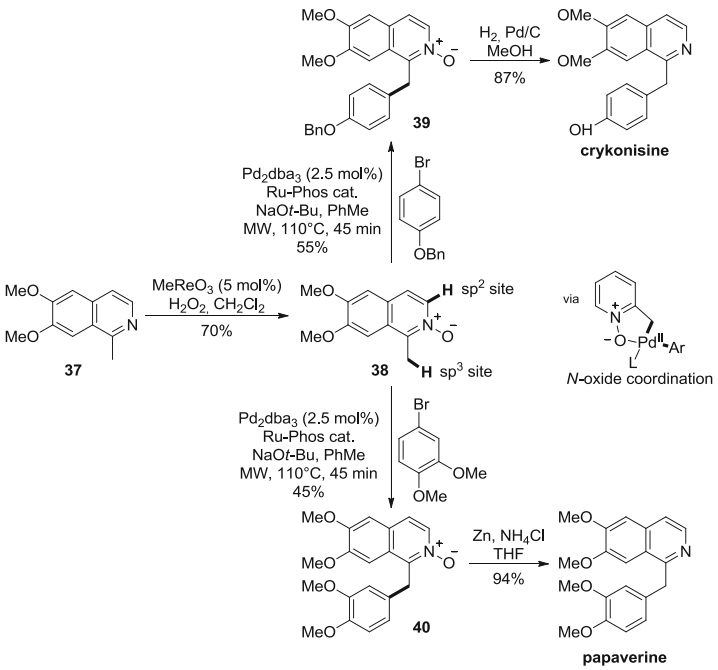
Only a few amine-derived directing groups have been reported, and all of them display drawbacks such as high reaction temperatures (typically 150°C) [59], difficult cleavage [20], or low accessibility [58]. On this basis, Fan and Ma reported a new 2-methoxyiminoacetyl (MIA) directing group for the γ-C(sp$^3$)-H arylation of amines, which is readily available, operates under moderate reaction temperatures, and can be removed under mild conditions to allow for further functionalization (Scheme 9) [61]. Using this directing group, they could perform the γ-C(sp$^3$)–H arylation of various 2-aminobutanoic acid derivatives with a broad range of aryl iodides. Furthermore, mild post-functionalizations such as room-temperature hydrolysis or hydrogenation provided homophenylalanine derivatives, which are important motifs in drug discovery, e.g., as peptidomimetics [64]. The synthetic utility of this protocol was demonstrated through the formal synthesis of the antihypertensive agent benazepril. Starting from the simple 2-aminobutanoic acid derivative **35**, lactam **36**, which directly intercepts the synthesis of Ciba-Geigy Corporation, was synthesized in only four steps and good overall yield.

## 2.4 Other Directed C–H Functionalizations

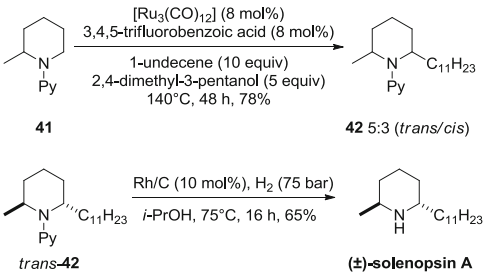
### 2.4.1 C–C Bond Formation

Fagnou and co-workers described a completely site-selective C($sp^3$)–H or C($sp^2$)–H arylation of a broad range of azine and diazine *N*-oxides with aryl halides, involving a $Pd^0/Pd^{II}$ catalytic manifold (Scheme 10) [65, 66]. This switch of regioselectivity is controlled by an intimidate involvement of the base and catalyst. Using a strong base like NaO*t*-Bu, the arylation, which is presumably directed by the *N*-oxide function, selectively occurred at the $sp^3$ site. This novel C($sp^3$)–H arylation methodology was applied to the total synthesis of the alkaloids crykonisine and papaverine, in only three steps after reduction of the *N*-oxide group, and starting from easily available materials.

In 2012, Maes and co-workers reported a new transition-metal-catalyzed methodology for the direct C2–H functionalization of piperidines [67], via pyridine-directed Ru-catalyzed C($sp^3$)–H alkylation with alkenes [68]. Based on previous work [69–73], they discovered that a combination of a bulky alcohol (2,4-dimethyl-3-pentanol) and a catalytic amount of a carboxylic acid [74] is necessary to avoid side reactions such as isomerization and/or reduction of the alkene reactant (Scheme 11). They successfully applied this method to the total synthesis of (±)-




**Scheme 10** Synthesis of crykonisine and papaverine via $Pd^0$-catalyzed site-selective C–H arylation of *N*-oxides




**Scheme 11** Synthesis of (±)-solenopsin A via Ru-catalyzed directed C–H alkylation

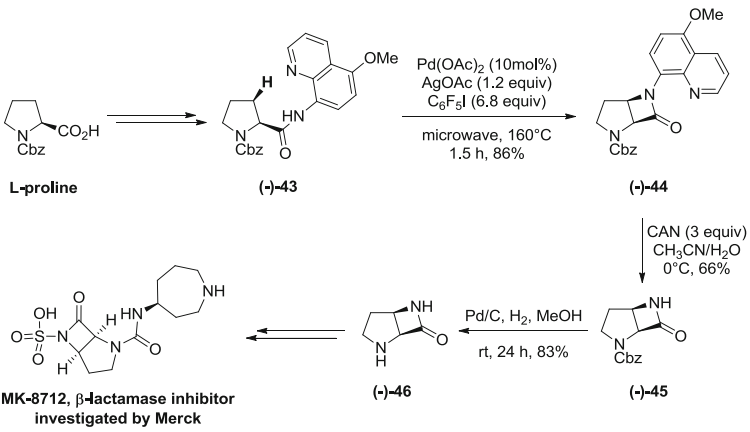
solenopsin A through a three-step sequence starting from racemic 2-methylpiperidine.

### 2.4.2 C–N Bond Formation

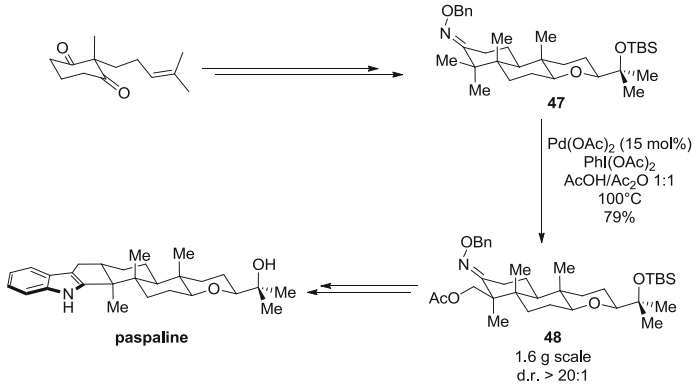
The formation of four- and five-membered *N*-heterocycles such as azetidines [38–40, 75] and β-lactams [36, 41] through direct C–N bond reductive elimination involving the nitrogen atom of amide directing groups is well documented. Building on these data, Wu and co-workers developed modified conditions to access β-lactams via Pd-catalyzed, $C_6F_5I$-assisted intramolecular amidation of β-C($sp^3$)–H bonds (Scheme 12) [42]. They found that a highly electron-deficient aryl iodide such as $C_6F_5I$ can promote the β-lactam formation pathway (C–N reductive elimination) over the arylation pathway (C–C reductive elimination). Using the 8-aminoquinoline directing group, they synthesized a broad range of β-lactams, including *cis*-fused systems which are difficult to access by other methods, with excellent yield and selectivity. To highlight the synthetic utility of this process, they reported the formal synthesis of β-lactamase inhibitor MK-8712. Starting from readily available L-proline, compound **43** containing the modified 5-OMe-quinoline, easily removable directing group introduced by Chen and co-workers [75] was obtained. The optimized intramolecular C–H amidation afforded *cis*-fused β-lactam **44** in 86% yield. Directing group cleavage with CAN and hydrogenolysis afforded the *cis*-fused product **46**, a key intermediate in the synthesis of the target β-lactamase inhibitor.

### 2.4.3 C–O Bond Formation

Sharpe and Johnson recently reported a stereocontrolled total synthesis of the indole diterpenoid paspaline (Scheme 13) [76]. In a key step, they envisaged to perform the C–H oxidation of diastereotopic *gem*-dimethyl groups, which would allow to install a pivotal quaternary stereocenter. Inspired by an initial report of Sanford and co-workers [77] and a seminal application in total synthesis by the group of Sorensen [78], they decided to carry out the key selective C–H oxidation of intermediate **47** containing an oxime directing group. Applying Sanford's original condition furnished the desired acetoxylated product **48** in high yield and as a




**Scheme 12** Synthesis of MK-8712 via Pd-catalyzed intramolecular C–H amidation

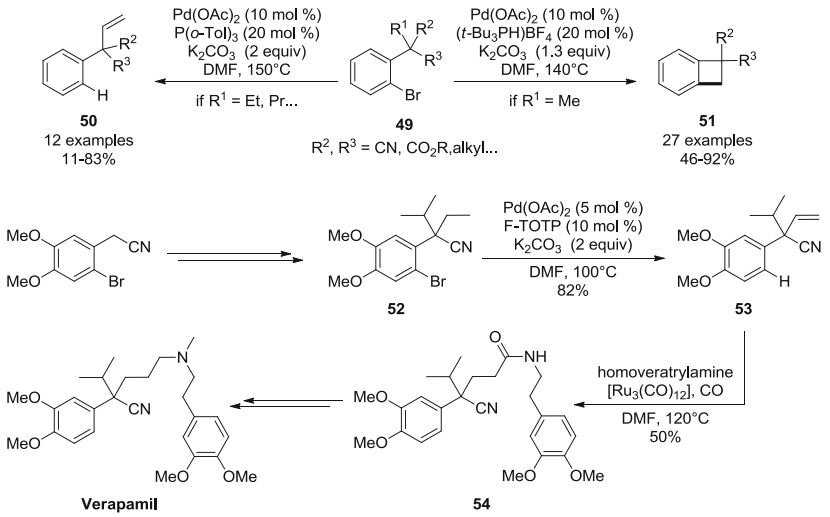



**Scheme 13** Synthesis of paspaline via diastereoselective oxime-directed C–H oxidation

single diastereoisomer. This complete diastereoselectivity is thought to originate from the favored conformation of **47**, which places the oxime C–N π-bond and the activated equatorial methyl group in the same plane. A 12-step sequence completed the stereocontrolled synthesis of paspaline.

## 3 Oxidative-Addition-Initiated C–H Activation

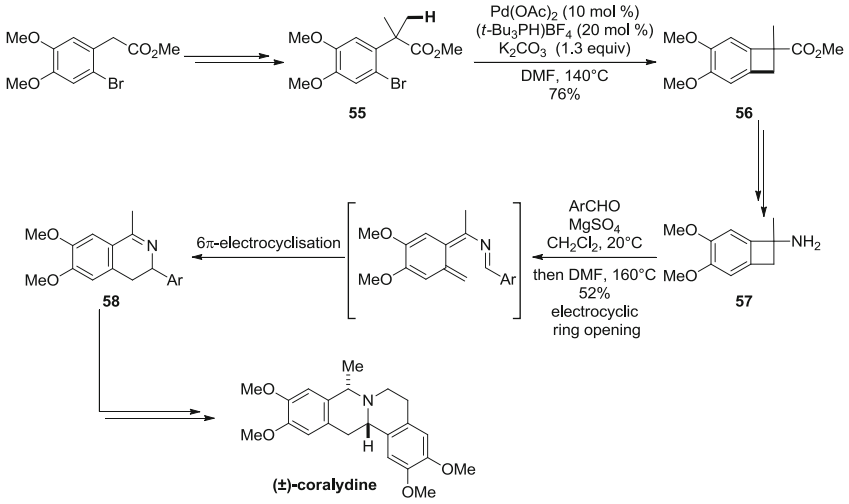
The oxidative addition of a carbon-leaving group bond to a low-valent transition-metal complex may play the same role as the binding to a Lewis basic directing group in order to trigger intramolecular C–H activation [2, 3]. Inspired by Dyker's C–H self-condensation of *ortho*-substituted aryl iodides under ligand-free conditions [79, 80], Baudoin and co-workers reported in 2003 the palladium(0)-catalyzed




**Scheme 14** Synthesis of verapamil involving a selective $Pd^0$-catalyzed formal dehydrogenation

C($sp^3$)–H functionalization of benzylic alkyl groups, giving rise to olefin **50** (formal alkane dehydrogenation) or benzocyclobutene **51** from aryl halide **49** (Scheme 14) [81]. In both cases, they found optimal conditions with DMF as the solvent and $K_2CO_3$ as the active base. Furthermore, in contrast to Dyker's initial work, no self-condensation was observed thanks to the use of suitable phosphine ligands. Indeed, the formation of olefins **50** was best performed using P(*o*-Tol)$_3$, whereas P(*t*-Bu)$_3$ was found to be optimal to construct benzocyclobutene **51** via a challenging C–C reductive elimination [82]. Further ligand design subsequently allowed to access a greater variety of linear and cyclic olefins under milder conditions [83]. To demonstrate the utility of the dehydrogenation method, the authors applied it to the synthesis of the calcium channel antagonist verapamil [83]. Thus, bromoarene **52**, easily obtained from a commercially available substituted phenylacetonitrile, was engaged into the optimized C–H activation procedure to afford the dehydrogenated product **53** in high yield and with high selectivity in favor of the ethyl *vs*. the isopropyl group. Verapamil was then obtained in good yield (six steps, 17% overall) through a three-step sequence involving ruthenium-catalyzed hydroamidation, *N*-methylation, and chemoselective reduction of the amide function.

In 2009, Baudoin and co-workers reported a new strategy for the synthesis of dihydroisoquinolines, involving sequential C($sp^3$)–H arylation and 6-π-electrocyclization, which was applied to the total synthesis of the tetrahydroprotoberberine alkaloid (±)-coralydine (Scheme 15) [84]. First, aryl bromide **55** underwent C–H activation/intramolecular C–C coupling to give benzocyclobutene methyl ester **56** in good yield. Hydrolysis of **56** followed by Curtius rearrangement yielded aminobenzocyclobutene **57**. Condensation of **57** with an appropriate substituted benzaldehyde afforded an imine intermediate, which was directly

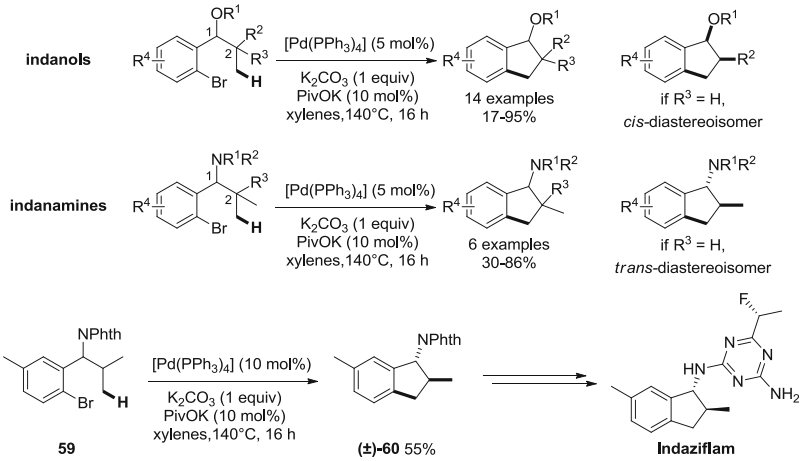



**Scheme 15** Synthesis of (±)-coralydine featuring $Pd^0$-catalyzed intramolecular C–H arylation

engaged in the key thermal tandem electrocyclic ring-opening/6-π-electrocyclization reaction [85], thereby providing dihydroisoquinoline **58** in 52% yield. An additional three-step sequence furnished (±)-coralydine, which was obtained with an overall yield of 6.2% in nine steps.

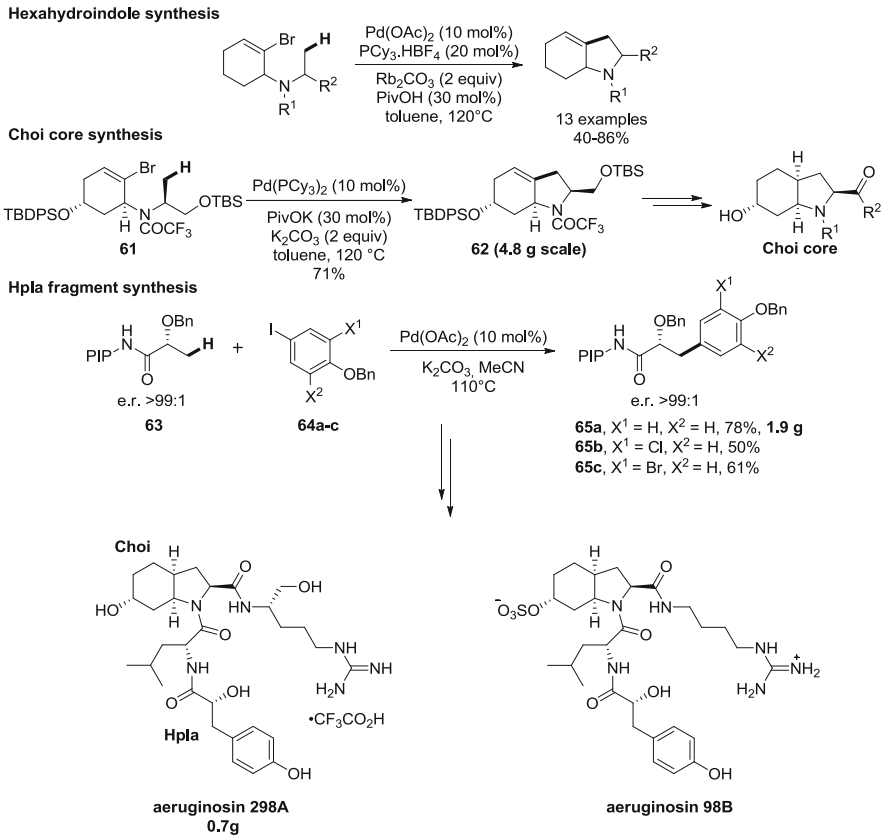
In 2014, the same research group described the synthesis of valuable 1-indanols and 1-indanamines through a similar intramolecular C–H arylation process (Scheme 16) [86]. In previous reports, (fused) indanes [83, 87, 88] and indanones [88] had been obtained, but only with a quaternary center at the C1 or C2 position, respectively. In the more recent study [86], Baudoin and co-workers proposed suitable conditions to synthesize more interesting, albeit more challenging indanes bearing a tertiary benzylic C1 carbon atom. 1-Indanols and 1-indanamines were obtained under operationally simple conditions and with moderate-to-high yield, depending on the degree of substitution at the C2 position, as a result of Thorpe–Ingold effects. Interestingly, the diastereoselectivity at C1 and C2 was affected by the nature of the heteroatomic substituent at C1. Indeed, a subtle conformational effect allowed to selectively obtain the *trans*-diastereoisomer in the 1-indanamine case, which is a valuable building block for the synthesis of APIs. In contrast, 1-indanols were obtained as the major *cis*-diastereoisomers. Within the framework of a collaboration with Bayer CropScience, this method was applied to the synthesis of racemic *trans*-aminoindane **60**, a known intermediate in the industrial synthesis of the herbicide indaziflam.

As an extension to C–H arylations, Baudoin and co-workers reported the intramolecular alkenylation of unactivated $C(sp^3)$–H bonds. Inspired both by Knochel's intramolecular $C(sp^3)$–H alkenylation of activated benzylic positions [89, 90] and by Ohno's indoline synthesis [91], they developed a unique route toward hexahydroindoles (Scheme 17) [92]. This method afforded $sp^3$-rich products in




**Scheme 16** Formal synthesis of indaziflam involving a conformationally challenging Pd$^0$-catalyzed intramolecular C–H arylation

good yield with a high degree of regioselectivity. More recently, the same authors reported its application to the synthesis of the bicyclic (Choi) core of aeruginosin marine natural products [93–95]. Cyclohexenyl bromide **61** which was obtained through a six-step synthesis from readily available precursors underwent C(sp$^3$)–H alkenylation on multigram scale under re-optimized conditions, to provide hexahydroindole **62** in good yield. In parallel, a rapid and divergent access to the hydroxyphenyllactic (Hpla) subunits of the natural products, including those containing chlorine or bromine atoms on the benzene ring, was developed, by using a palladium-catalyzed directed β-C–H arylation of a D-lactic acid derivative (**63**). After screening various directing groups and reaction conditions, the 2-pyridinylisopropyl (PIP) group introduced by Shi and co-workers [41] was found to be the best option to furnish the various required Hpla subunits **64a–c** in good yield and without erosion of optical purity. A multistep sequence involving peptide coupling and deprotections allowed to complete the total synthesis of aeruginosins 98B and 298A, with an unprecedented overall yield and scale for the latter (0.7 g, 8.2% overall yield), and started from simple chiral pool precursors [93]. This strategy also allows to synthesize aeruginosin congeners bearing halogen atoms on the Hpla subunit [94]. This final application highlights the synthetic power of C(sp$^3$)–H activation, when employed in a strategic manner to streamline complex molecule synthesis.




**Scheme 17** Total synthesis of aeruginosins featuring two strategic Pd-catalyzed C–H activation reactions

## 4 Conclusion

In the past decade, catalytic organometallic C($sp^3$)–H activation has undergone major progress and has become a powerful tool to create C($sp^3$)–X bonds in a very direct manner. An increasing number of applications of the newly developed methods have been reported, both in natural product and API synthesis. The use of C–H bond functionalization in a strategic manner in retrosynthetic analysis is an emerging concept that will deeply impact organic synthesis on the long term, by improving atom and step economy and thus overall efficiency. However, the field is still in its infancy, as one is far from being able to selectively functionalize a given C–H bond in a given organic molecule, and many exciting developments and applications lie ahead.

**Acknowledgments** The authors thank Région Rhône-Alpes (ARC Santé) and Fondation Pierre Potier pour le Développement de la Chimie des Substances Naturelles et ses Applications for financial support.

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